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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,285	07/03/2003	Richard Derek Iggo	604-689	5824

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,285	IGGO ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2006 and 24 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 10/24/06 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 602.

The declaration filed 11/27/06 states that the instant application was filed as PCT/GB02//03211. This is incorrect. The instant application is a continuation-in-part of 10/433,681, which was filed as PCT/GB02//03211. Since this application is a CIP of the '681 application, it clearly was not filed as PCT/GB02//03211.

Specification

The disclosure is objected to because of the following informalities. A paragraph containing priority information, which was incorrect, was inserted as the first line of the specification in the preliminary amendment filed 7/3/03. Subsequently in the amendment of 10/24/06, a second paragraph containing priority information, which is correct, was inserted after the title, but without deleting the previously added paragraph. As a result, the specification has been amended to include two separate paragraphs containing priority information, one correct and one incorrect. The paragraph added by preliminary amendment on 7/3/03 should be cancelled.

Appropriate correction is required.

Claim Objections

Claims 1 and 21 remain objected to because of the following informalities. Claim 1 is poorly punctuated such that different elements of the claim run together. For example, in line 2, a comma should follow "cell," the semi-colon in line 10 does not separate members of a list, etc. In claim 21, "Tcf-4, RBPJK, Gli-l, HIFlalpha and" should be "Tcf-4, RBPJK, Gli-l, and HIFlalpha binding sites, and--. Tcf-4, RBPJK, Gli-l, and HIFlalpha are proteins, not DNA sequences. Appropriate correction is required.

Applicant indicates in the reply of 10/24/06 that claim 21 had been amended. However, claim 21 was not amended.

Claims 2-8, 11, 21 and 22 are objected to because of the following informalities. Recitation of an indefinite article, e.g. "A", at the beginning of these dependent claims is improper grammar, and should be replaced with the definite article --The--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to require that the packaging signal be relocated to the right end of the adenovirus. Claim 4 also indicates the packaging signal be relocated but may be relocated anywhere in the adenovirus. There are two possible interpretations of the scope of claim 4 (see rejection under § 112, second paragraph, below). One of these is that the adenovirus has two packaging signals, the first relocated as recited in claim 1, and the second relocated anywhere in the adenovirus. This constitutes new matter, as there is no support in the original disclosure for an adenovirus with two packaging signals.

Claims 1-11, 21, and 22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action of 3/7/06 and the new reasons added below. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

First, claim 1 recites the limitation: "a similar number of the one or more of the human or animal transcription factor binding sites to those inserted with the E1A open reading frame being inserted into the right hand inverted terminal repeat (ITR) such as to provide sufficient symmetry to allow it to base pair to the left hand ITR during replication." This feature is originally described (page 5, lines 12-26; page 7, line 23, to page 8, line 13; Fig. 1A) in the context of an embodiment where endogenous transcription factor binding sites upstream of the E1A coding region of the adenoviral genome, including those within the 5' ITR, are replaced with exogenous transcription factor binding sites, the packaging sequence is moved to another operable location, e.g. near the 3' ITR, and the 3' ITR is modified by making the same replacements of transcription factor binding sites as done with the 5' ITR, in order to "provide sufficient symmetry". The movement of the packaging sequence is required in the disclosed embodiment because replacement of the binding sites within the E1A enhancer would also be replacement of parts of the packaging sequence, which would inactivate the packaging sequence. As amended, claim 1 still does not require that transcription factor binding sites in the left hand ITR are substituted with the human or animal transcription factor binding sites. Not all of the endogenous transcription factor binding sites that are upstream of the E1A open reading frame are in the 5' ITR. Thus, the claim as written is directed to a broader genus than was described in the original disclosure because it does not include the other limitations of the originally described embodiment to which this new claim limitation pertains, namely that binding sites in the 5' ITR are substituted.

Second, claim 1 recites the limitation the viral DNA construct "further comprises unmodified wild type transcription factor binding sites for the E2 and E3 open reading frames." This limitation as amended still does not specify where these wild type binding sites are located, i.e. these binding sites need not be in their endogenous locations in the E2 and E3 regions of the wild type adenovirus DNA sequence. Recitation of "further comprises" implies that they are added, rather than endogenous. The specification discloses that the endogenous overlapping, divergent E2 and E3 promoter region of the adenoviral DNA may also be modified by mutations to inactivate endogenous transcription factor binding sites (E3) and/or by insertion of the exogenous human or animal transcription factor binding sites (page 6, lines 17-23), which implicitly means that they need not be modified. The specification does not disclose moving or inserting these endogenous transcription factor binding sites of the E2 and E3 regions to other locations in the construct, as is permitted by the claim as written. This part of the rejection would be overcome by amending the claim to clearly require that the E2 and E3 transcription factor binding sites of the wild type adenovirus DNA sequence are not modified. It is suggested that the phrase "wherein the viral DNA construct further comprises ... E2 and E3 open reading frames" in lines 14-16 of claim 1 be replaced with --; wherein the transcription factor binding sites of the E2 and E3 open reading frames of the wild type adenovirus DNA sequence are not modified-- along with suitable amendment to provide a lead-in in line 16 for the next limitation.

Applicant simply asserts that the rejection has been overcome by the amendment.

Claims 1-11, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "similar number" in claim 1, line 10, is a relative term which renders the claim indefinite. The term "similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how close to the number of inserted binding sites at the 5' end are required to be a "similar number" with respect to the 3' end.

Claim 1 recites the limitation "the one or more human or animal transcription factor binding sites to those inserted with the E1A open reading frame" in lines 10-12. There is insufficient antecedent basis for this limitation in the claim. The claim does not indicate that binding sites are "inserted with the E1A open reading frame" nor is it clear what the phrase "inserted with the E1A open reading frame" means.

Claim 1 recites the limitation "the adenoviral sequence" in the last line. There is insufficient antecedent basis for this limitation in the claim. Replacing this phrase with --the wild type adenovirus DNA sequence-- would be remedial.

Claim 1 has been amended to require that the packaging signal be relocated to the right end of the adenovirus. Claim 4 also indicates the packaging signal be relocated but may be relocated anywhere in the adenovirus. There are two possible interpretations of the scope of claim 4. First, the adenovirus has two packaging signals, the first relocated as recited in claim 1, and the second relocated anywhere in the adenovirus, which as indicated above is new matter.

Second, the relocated packaging signal referred to in claim 4, is the same relocated packaging signal referred to in claim 1, i.e. there is only one packaging signal. Claim 4 is ambiguous as to which of these interpretations is correct. If the second alternative is correct, then claim 4 does not further limit the scope of claim 1, since the orientation of the packaging signal is implicitly the same or reverse of the wild type orientation. Claim 4 simply lists the two possible orientations, as consequently would not further limit claim 1. Consequently Applicant is advised that should claim 1 be found allowable, claim 4 would be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Either way, claim 4 should be cancelled.

Claims 1-11, 21, and 22 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons of record set forth in the Office action of 3/7/06.

Claim 1 recites the limitation "the adenovirus E1A open reading frame" in line 5. There is insufficient antecedent basis for these limitations in the claim. Insertion --of the wild type adenoviral DNA sequence-- following "frame" would provide the antecedent basis.

Claim 1 recites the limitations "the adenovirus fibre gene and the adenovirus E4 region" and "the E3 promoter" in lines 18-20. There is insufficient antecedent basis for these limitations in the claim. This would be remedied by deleting "of the viral construct" (line 15) and inserting -

-in the adenoviral DNA sequence-- after "consisting of a location" in line 18. The claim was not amended as suggested, the phrase was inserted after "location" in line 15 rather than in line 14 as suggested.

Claim 1 recites the limitation "one or more of the human or animal transcription factor binding sites being inserted into the right hand inverted terminal repeat (ITR) such as to provide sufficient symmetry to allow it to base pair to the left hand ITR during replication." This limitation is unclear and ambiguous since the claim does not recite any modification of the left hand ITR. Consequently, it is unclear "symmetry" is being referred to or what modifications are being required in the right hand ITR, or whether the claim actually requires symmetrical modifications to the left and right hand ITRs.

Claim 8 recites the limitations "the E4 promoter," "the E1A enhancer," and "the packaging signal" in lines 1-2. There is insufficient antecedent basis for these limitations in the claim.

Applicant's arguments filed 10/24/06 have been fully considered but they are not persuasive. Applicant indicates that the amendments have overcome the previous grounds of rejection. In response, the amendments have overcome some, but not all, of the grounds of rejection.

Claim Rejections - 35 USC § 102

Claims 1, 3, 4, 7, 9-11, 21, and 22 remain rejected under 35 U.S.C. 102(b) as being anticipated by Iggo et al., WO 00/56909 for the reasons of record set forth in the Office action of 7/11/05.

Applicant's arguments filed 10/22/06 have been fully considered but they are not persuasive. With respect to the rejection over Iggo, Appellant argues that Iggo limits the early genes whose promoter may be altered to those of the E2 region, arguing that "mechanistically directly involved in viral construct nucleic acid replication" excludes E1A. Iggo, page 8, lines 3-8, teaches that the region whose promoter is altered "may be" the region encoding the polymerase, etc. Since expression of the E1A region is required for activation of the genes encoding the polymerase etc., it is mechanistically directly involved in replicating the viral genome. Also, one explicitly described alternative is modification of the E1B promoter alone, or with additional modifications to the E2 or E1A promoters. The instant claims do not exclude modification of both the E1A and E1B promoters, as suggested in Iggo, page 13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, 7, 9-11, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al., US 6,197,293 in view of Iggo et al., WO 00/56909.

Henderson, which is assigned to Calydon, describes recombinant adenovirus (Calydon virus) for treatment of cancer by killing cancer cells infected with the adenovirus. The adenovirus have the E1A region of the adenovirus placed under control of a heterologous transcriptional regulatory element (TRE) that functions in cancer cells, e.g. a TRE of a probasin gene, human kallikrein-1 gene, or prostate specific antigen gene, but not in most normal cells. Henderson primarily teaches inserting the TRE into the promoter region of the E1A region, but also teaches generally removing endogneous adenoviral TREs to make more room for inserts and modifying promoters of other essential adenoviral genes, e.g. E1B, with the heterologous TREs. Henderson also teaches inserting heterologous transgenes into the vector, such as genes encoding therapeutic gene products, e.g. HSV thymidine kinase and cytosine deaminase. See entire document, especially the abstract, col. 22, lines 24-31; col. 24, lines 13-46; col 26, line 56, to col. 27, line 7;col. 30, line 65, to col. 31, line 13; claims 1, 2, 23, 25, and 44-47. Henderson does not teach replacing endogenous TREs found in the ITRs with the heterologous TREs, or moving the packaging signal to the 3' end of the adenovirus.

However, Iggo et al. discloses a DNA construct encoding an adenoviral genome that generically has one or more early viral genes, e.g. E2 genes or E1B genes, under control of a promoter comprising one or more heterologous transcription factor binding sites that binds a

transcription factor that is expressed at higher levels in a tumor cell than in a normal cell of the same type, such as a Tcf-4, RBPJk, Gli-1 or HIFα transcription factor binding site or a part of a telomerase promoter that confers tumor–specific transcription, and using same for treating cancer. Iggo teaches using the adenovirus for treating patients having neoplasms, such as colon cancer and liver metastases of colon cancers wherein the heterologous transcription factor binding site is a Tcf-4 binding site. The heterologous transcription factor binding site may replace wild-type viral promoter sequences, and multiple copies of the binding site may be inserted, e.g. 2-20 copies of a Tcf-4 binding site. The adenoviral genome may be derived form Ad5, Ad40 or Ad41, or incorporate DNA encoding an Ad40 or Ad41 fiber protein. The adenoviral genome preferably retains a functional viral RNA nuclear export capability by retention of the E1B 55k protein gene and E4 ORF6. In some embodiments (page 13), the E1A promoter is also modified wherein the heterologous binding sites replace regulatory sequences in the E1A promoter including those in the 5' ITR to further restrict replication of the adenovirus to tumor cells. In these embodiments, the packaging sequence, which has overlapping E1A promoter sequences, is moved to the right ITR, which is adjacent to the E4 promoter and the right ITR is also modified with the transcription factor binding sites to preserve symmetry. A therapeutic gene, such as a gene encoding a prodrug activating enzyme such as HSV tk or cytosine deaminase, can be included in the adenoviral genome under control of the E3 promoter, which is regulated in a replication-dependent manner normally by E1A, and when E1A is under control of a heterologous transcription factor binding site. At page 13, Iggo teaches that the disclosed modification of the E1A promoter to that of "the Calydon viruses" and teaches that it provides space for insertion of transgenes than with the Calydon vector design such that all

adenoviral coding regions can be retained. See entire document, especially pages 6-17, 22-31, and claims 1-36.

Therefore, it would have been obvious to one of ordinary skill in the art to at the time the invention was made to have modified the E1A promoter region of the adenovirus of Henderson (a Calydon virus) as taught by Iggo for the reasons that Iggo teaches, i.e. to provide space for the insertion of therapeutic genes while retaining all adenoviral coding sequences.

Double Patenting

Claims 1-11, 21, and 22 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7, 9, 11-16, 19, 20, and 25-38 of copending Application No. 10/433,681 for the reasons of record set forth in the Office action of 7/11/05. The claims as amended in the instant and copending applications are directed to the same disclosed embodiments, although the claims do not precisely match in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has acknowledged the rejection but has declined to address it until prosecution has otherwise been completed in the two applications. Applicant is advised of recent changes to procedures involving provisional obviousness-type double patenting rejections involving copending applications, see MPEP 804, subsection I.B.1. In a situation like this one, a proper provisional rejection in the junior application may not be withdrawn so long as the senior

application is pending, even if junior application is otherwise in condition for allowance, but the senior application is not.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Scott D. Priebe

Scott D. Priebe, Ph.D.
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Art Unit 1633